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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/516,741	08/15/2005	Thomas Jespersen	4528-0109PUS2	6986

2292 7590 06/18/2008

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EXAMINER	
WESSENDORF, TERESA D	

ART UNIT	PAPER NUMBER
1639	

NOTIFICATION DATE	DELIVERY MODE
06/18/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

mailroom@bskb.com

Office Action Summary	Application No.	Applicant(s)	
	10/516,741	JESPERSEN ET AL.	
	Examiner	Art Unit	
	T. D. Wessendorf	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 April 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3 and 7-14* is/are pending in the application.

4a) Of the above claim(s) *3 and 14* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3 and 7-14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 4/7/2008 has been entered.

Status of Claims

Claims 1-3 and 7-14 are pending.

Claims 3, 10 (with respect to the non-elected species), 12 (with respect to the non-elected species) and 14 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention.

Claims 1-2 and 7-13 are under examination.

Withdrawn Rejection

In view of the amendments to the claims and applicants' arguments the 35 USC 112 second paragraph rejection has been withdrawn.

Claim Rejections - 35 USC § 112

Claims 1-2 and 7-13, as amended, are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

New Matter Rejection

Claim 1 drawn to **"the mRNA is isolated without removing the cell from the substrate", "the mRNA transcribed therefrom"** and **"simultaneous" detection** are not supported in the as-filed specification. Applicants referred to Figures 2 and 3 and Example 6 as support for the various amendments to claim 1. However, Fig. 2 states:

> Figure 2- Schematic diagram showing a single target cell positioned in the test site on the chip. The cell expresses a single genomic construct. Below the cell is a small opening between the test site and well, the cell membrane at this site is perforated or removed for electrophysiological analysis. Other phenotype analyses are shown (dotted lines). Genotype detection is also conducted **by extraction of the mRNA via the opening over which the cell membrane is incomplete.** Figure 3 - Schematic diagram of the preferred chip construct. (Emphasis added).

Thus, it is not apparent from Figure 2 as to the DNA transcription from mRNA or from Fig. 3 description of the chip

construct. There is nothing in Example 6 to support the present amendments to the claims.

Written Description

The specification fails to provide an adequate written description of the invention. The specification provides only prophetic statements and general statements of the claimed method. There is no description as to the kind of the different types of cells that express different kinds of DNA or mRNA or other genetic materials. The specification does not describe from the numerous DNA expressed by a single cell, let alone from a plurality of cells, the heterologous ones that caused an electrophysiological change(s) in a cell. More importantly how each heterologous DNA can be differentiated from one another such that each DNA expresses an electrophysiological effect on each cell. There is not a single example to demonstrate the huge scope of the claimed method. Examples might not be required for a highly explored art as mechanical. However, for a highly unexplored art as gene expression in cells where one cannot predict a priori if the desired DNA has been expressed by the cell, example is almost required. It is well known in the art, that it is often difficult to determine whether a heterologous DNA is

efficiently expressed by a particular expression system. And, it is not always easy to follow the expression of the heterologous DNA in particular cells; for example, to know whether or not a specific cell is expressing a member of the insert, especially for biological methods. Thus, the prophetic and general statements in the specification are not adequate description of the claimed method having such huge scope.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-2 and 7-13, as amended, are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. Claim 1 is being incomplete for omitting essential steps and/or elements, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: the steps by which a cell of interest can be identified by its electrophysiological effect by the mere providing of a substrate on a plurality of cells and arranging the plurality of cells on

the substrate. It is not clear how the heterologous DNA is expressed such that the cell undergoes electrophysiological changes. Furthermore, it is unclear as to the heterologous DNA and the transcription of mRNA occurring in the cells.

B. The claimed a “heterologous DNA sequence” is unclear, within the claimed context, as to the scope of the heterologous DNA sequence in the different plurality of cells especially in the absence of positive definition/support in the specification.

C. “The cell of interest” is unclear as to the basis or standard by which one bases the cell of interest especially in the absence of positive support in the specification.

D. It is unclear as to the “genetic material” the cell of interest that is being refereed to. Is this the mRNA or heterologous DNA (See Fig. 2 above, which refers only to mRNA and not genetic material). Thus, there is an inconsistency in what is being claimed.

E. Claim 2 is unclear as to the positive step required for the "step of sequencing the genetic material" given no genetic material specifically referred thereto. It is suggested that applicants recite a positive step rather simply the term “step".

F. In claim 7 “each different heterologous DNA sequence is part of a cDNA library” is confusing as to how the DNA sequence

is only a part rather than the cDNA library itself i.e., that the DNa is a cDNA library.

G. Claim 13 "spaced-apart" locations are indefinite as to how or what the spacing of the cells is such that each is apart from each other. This term is a relative term. It is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

Claim Rejections - 35 USC § 102/103

Claims1-2 and 7-13, as amended, are rejected under 35 U.S.C. 102(e) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Qin (6994993).

Qin discloses throughout the patent e.g., at col. 20, line 1 up to col. 22, line 50:

> The present invention provides a whole cell or isolated cell membrane method to detect compound modulation of human .beta.1A sodium channel subunit.
>
> The method comprises the steps;
>
> 1) contacting a compound (test agent, as recited in claim 9), and a cell or isolated cell membrane that contains functional human .beta.1A sodium channel subunit, and
>
> 2) measuring a change in the cell or isolated cell membrane in response to modified human .beta.1A sodium channel subunit function by the compound.

The measurement means… can be defined by comparing a cell or cell membrane that has been exposed to a compound to an identical cell or cell membrane preparation that has not been similarly expose to the compound. Alternatively two cells, one containing functional human .beta.1A sodium channel subunit and a second cell identical to the first, but lacking functional human .beta.1A sodium channel subunit could be both used. Both cells or cell membranes are contacted with the same compound and compared for differences between the two cells.

Particularly preferred cell based assays (or cell membrane assays, if suitable) are those where the cell expresses an endogenous or recombinant sodium .alpha. channel subunit simultaneously with recombinant human .beta.1A(heterologus DNA expression of cell, as claimed). In these assays, a putative modulating compound can be analyzed for its effect on electrophysiological changes to the sodium flux upon the cell for altered expression of beta1A expression, or altered expression of the alpha/beta1A complex. Cells expressing recombinant human beta 1A are subjected to electrophysiological analysis to measure the total influx of sodium ions across the cell membrane by way of voltage differential using techniques well known by artisans in the field and described herein, including patch clamp voltage techniques …... Compounds that affect the proper function of human beta 1 may increase or decrease the capacity to open the Na channel, may increase or decrease the rate of Na influx (thus affect the change of membrane potential), may increase or decrease the rate of desensitization or re-sensitization of the channel. The term "test compound" or "modulating compound" as used herein in connection with a suspected modulator of human beta1A refers to an organic molecule that has the potential to disrupt specific ion channel activity or cell surface expression of human beta 1A. For example, but not to limit the scope of the current invention, compounds may include small organic molecules, synthetic or natural amino acid peptides, proteins, or synthetic or natural nucleic acid sequences, or any chemical derivatives of the aforementioned.

The term "cell" refers to at least one cell, but includes a plurality of cells appropriate for the sensitivity of the

detection method. Cells suitable for the present invention may be bacterial, yeast, or eukaryotic. For assays to which electrophysiological analysis is conducted, the cells must be eukaryotic, preferably selected from a group consisting of Xenopus oocytes, or PC12, COS-7, CHO, HEK293, SK-N-SH cells.

The term "high throughput" refers to an assay design that allows easy analysis of multiple samples simultaneously, and capacity for robotic manipulation…..Examples of assay formats include 96-well or 384-well plates, levitating droplets, and "lab on a chip" microchannel chips used for liquid handling experiments.

The cellular changes suitable for the method of the present invention comprise directly measuring changes in the function or quantity of human.beta.1A sodium channel subunit, or by measuring downstream effects of human beta.1A sodium channel subunit function, for example by measuring secondary messenger concentrations or changes in transcription or by changes in protein levels of genes that are transcriptionally influenced by human beta.1A sodium channel subunit, or by measuring phenotypic changes in the cell. Preferred measurement means include changes in the quantity of human beta.1A sodium channel subunit protein, changes in the functional activity of human beta.1A sodium channel subunit, changes in the quantity of mRNA….. **Changes in the levels of mRNA are detected by reverse transcription polymerase chain reaction (RT-PCR) or by differential gene expression.**

The present invention is also directed to methods for screening for compounds that modulate the expression of DNA or RNA encoding Human beta.1A sodium channel subunit as well as the function of Human beta.1A sodium channel subunit protein in vivo. Compounds may modulate by increasing or attenuating the expression of DNA or RNA encoding a Human beta.1A sodium channel subunit, or the function of a Human beta.1A sodium channel subunit protein. Compounds that modulate the expression of DNA or RNA encoding a Human beta.1A sodium channel subunit or the function of a Human beta.1A sodium channel subunit protein may be detected by a variety of assays.

See also the abstract and the specific steps of the method in the Examples starting at col. 29, Example 1. (All emphasis added).

Response to Arguments

Applicants state that none of the cited documents describe the analysis of multiple different DNA molecules as part of the same assembly. Each of these documents describes the analysis of cells (either singly or multiple cells) each containing the same heterologous DNA expressing a single defined ion channel.

In response attention is drawn to the Qin reference above which states:

> Particularly preferred cell based assays (or cell membrane assays, if suitable) are those where the cell expresses an endogenous or recombinant sodium .alpha. channel subunit simultaneously with recombinant human .beta.1A.

Thus, a recombinant sodium alpha channel subunit is different from a recombinant human beta IA subunit, which reads on multiple different DNA heterologous molecules as argued and claimed. Furthermore, it would be within the ordinary skill in the art to determine the numbers of heterologous DNA that are expressed by the different cells. Qin teaches above a plurality of cells as assayed using any

of the art method of 96-well or 384-well plates, levitating droplets, and "lab on a chip" microchannel chips. (This is especially true since the specification provides no more than prophetic statements as to the claimed method steps).

Claims 1-2 and 7-13, as amended, are rejected under 35 U.S.C. 102(e) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Maher (6969449).

Maher discloses at e.g., col. 12, line 30 up to the Examples, particularly Example 10:

1) Instrumentation including electrodes, and electrode arrays for reliably generating uniform electrical fields in cultures of living cells in aqueous solution.

2) Multiwell plates comprising surface electrodes for high throughput and miniaturized stimulation and analysis of ion channel or cellular activities.

3) Systems for high throughput analysis of ion channel and cellular activities and for use in drug discovery, analysis, screening and profiling.

4) Methods for modulating the transmembrane potential of a living cell via the use of repetitive electrical stimulation.

5) Methods for screening the effects of test compounds on the activities of voltage regulated, and non-voltage regulated ion channels, transporters and leak currents. Including determining state-dependent pharmacological activity of compounds against ion channel and transporter proteins.

6) Methods for profiling and selecting cells or clones based on their response to electrical stimulation.

7) Methods for quantitative determination of cellular and ion channel parameters in a high-throughput manner, and for quantification of the pharmacological effects of compounds on those parameters.

8) Methods for the introduction of exogenous compounds into the intracellular spaces of cells.

9) Methods for modulating the transmembrane potential of intracellular organelles, and for screening test compounds against ion channels in these organelles.

10) Methods for characterizing the physiological effect of the transmembrane potential on the function and regulation of physiological and biochemical responses, including gene expression, enzyme function, protein activity and ligand binding.

11) Methods for programming or training adaptive neuronal networks or bio-computers for specific functional or logical responses.

12) Methods for providing efficient neuronal interfaces for prosthetic devices implanted into an animal, including a human.

Selection of stable clones will typically be made on the basis of successful expression of the ion channel of interest at sufficient level to enable it's facile detection. **In many cases this analysis will require functional characterization of individual clones to identify those that exhibit appropriate electrophysiological characteristics consistent with expression of the clone of interest. This analysis can be completed via the use of patch clamping** ……..

The invention also provides non-human animals expressing one or more hybrid olfactory receptor sequences of the invention, particularly human olfactory receptor sequences. Such expression can be used to determine whether a test compound specifically binds to a mammalian olfactory transmembrane receptor polypeptide in vivo by contacting a non-human animal stably or transiently infected with a **nucleic acid derived from the library of the invention with**

a test compound and determining whether the animal reacts to the test compound by specifically binding to the receptor polypeptide.

Response to Arguments

Applicants did not argue the Maher reference separately from the Qin reference above. Accordingly, the response above is applied herein. In addition to the above arguments, applicants' attention is drawn to the entire disclosure of Maher at **e.g.,** col. 77, Example 17 which discloses the screening of multiple channels of sodium, calcium, potassium in a multiple cells of HL5. Furthermore, Maher discloses the different types of cells that express the different channels. Likewise, Qin teaches or at least suggests that sodium gated/31A subunits which would read on the claimed library. Furthermore, Qin teaches as stated above the measurement using mRNA.

Thus, each of the cited prior art either positively teaches, at least suggests, plurality of cells transfected by different heterologous genes of ion channels as taught by Maher or can be implied by the teachings of Qin using different subunits. Qin above, for example, teaches that ".measurement means include changes….. in the quantity of mRNA….. **Changes in the levels of mRNA are detected by reverse transcription**

polymerase chain reaction (RT-PCR) or by differential gene expression.

Claims 1-2 rejected under 35 U.S.C. 103(a) as being unpatentable over Qin or Maher in view Hutchens (6818411).

Each of Qin and Maher is discussed above. Each of the references, as argued above, is alleged not to teach the step to isolate the mRNA from the cell while the cell is still positioned on the substrate. (Note however, as stated above, that this is at least suggested by each of Qin or Maher). However, Hutchens discloses throughout the patent at e.g., col. 2, line 60 up to col. 3:

> ….Methods for retentate chromatography. Retentate chromatography is a combinatorial method to provide high information resolution of analytes in complex mixtures through the use of multi-dimensional separation methods. It provides a unified analyte detection and functional analysis capability for biology and medicine that is characterized by a single, integrated operating system for the direct detection of analyte expression patterns associated with gene function, protein function, cell function, and the function of whole organisms. In one aspect, this invention provides a unified operating system for the discovery or diagnosis of gene function, protein function, or the function of entire macromolecular assemblies, cells, and whole organisms.

Accordingly, it would have been obvious to one having ordinary skill in the art at the time the invention was made to analyze the expressed gene, mRNA in situ in the method of either Qin or Maher as taught by Hutchens. The

advantage in the retentate chromatography i.e., analyzing gene expression on site on a substrate as taught by Hutchens would provide the motivation to one having ordinary skill in the art at the time the invention was made. One would have a reasonable expectation of success since Hutchens teaches that several genes expressed by cells has been detected in site i.e., without removing the expressed genes on the substrate.

Conclusion

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Fisher (6897031) discloses multiparameter FACS assays to detect alterations in cells.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to T. D. Wessendorf whose telephone number is(571) 272-0812. The examiner can normally be reached on Flexitime.

If attempts to reach the examiner by telephone are unsuccessful, the examiner’s supervisor, James Schultz can be reached on (571) 272-0765. The fax phone number for the organization where this application or proceeding is assigned is 571 273-8300. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about

the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/T. D. Wessendorf/

Primary Examiner, Art Unit 1639